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Further evidence that chick eyes use the sign of blur in spectacle lens compensation

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Abstract

Young animals compensate for defocus imposed by positive or negative spectacle lenses by adjusting the elongation rate of their vitreous chambers, thus matching the length of the eye with the focal length of the eye's optics combined with the spectacle lenses. The ability to compensate for either negative or positive lenses could rely on the ability to distinguish between myopic and hyperopic blur, or it could rely on the fact that positive lenses would bring nearby objects into focus, thereby reducing the amount of blur, whereas negative lenses would not. This study asks whether eyes emmetropize using the magnitude of blur or the sign of blur as a directional cue.

We fitted chick eyes with positive lenses while imposing a substantial amount of blur, either (a) by having them wear lenses only when restrained in the center of a cylinder, the walls of which were beyond their far-point or (b) by having them wear mild diffusers over positive lenses. We found good refractive compensation in both situations in a large number of birds. Furthermore, we found that mild diffusers worn on top of positive lenses differentially affected the two ocular components of refractive compensation: there was less choroidal thickening, but more inhibition of ocular elongation, compared to wearing positive lenses alone. These findings argue both that the eye can discern the sign of the blur and that choroidal and ocular-elongation components of the refractive compensation do not respond identically to visual inputs.

Keywords: Defocus; Emmetropization; Hyperopia; Myopia; Ocular refraction; Choroid

1. Introduction

In a matter of days, the eyes of chicks can grow to correct a wide range of refractive errors. If chicks wear +15 to −10 D spectacle lenses, the imposed defocus can be fully compensated for in a week by changes in the elongation rate of the eye and in the thickness of the choroid (Irving, Callender, & Sivak, 1991; Schaeffel, Glasser, & Howland, 1988; Wallman et al., 1995; Wildsoet & Wallman, 1995). If chicks wear stronger lenses of either sign, compensation falls off (Irving, Sivak, & Callender, 1992; Nevin, Schmid, & Wildsoet, 1998).

The fact that eyes compensate for either positive or negative lenses would seem to imply that the emmetropization mechanism has the ability to detect the sign of defocus, that is, whether the image is focused in front of or behind the retina. Although in a perfect optical system defocus contains no sign information, in the case of the eye, longitudinal chromatic aberration, spherical aberration, astigmatism and other aberrations might help the eye distinguish myopic from hyperopic defocus. However, attempts to identify which cues the eye uses have been unsuccessful (McLean & Wallman, 2003; Rohrer, Schaeffel, & Zrenner, 1992; Schaeffel & Diether, 1999; Schmid & Wildsoet, 1996; Wildsoet, Howland, Falconer, & Dick, 1993) raising doubt about whether the eye actually has the ability to discern the sign of defocus.

Alternatively, the amount of defocus, regardless of sign, might determine the rate of ocular elongation. This alternative is attractive because it does not require the emmetropization system to determine the sign of defocus. Because accommodation is imperfect, near objects would be slightly blurred; negative lenses would increase this blur, and, as a result, might increase ocular

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elongation. Positive lenses, on the other hand, would reduce blur if the animals looked primarily at near objects, and this reduced blur might slow ocular elongation (Norton & Siegwart, 1995). Thus, in lens-compensation experiments, positive lenses could be effective either because they increase the sharpness of images or because they impose myopic blur. In this paper we ask which factor is the relevant one.

Evidence that the eye might emmetropize by using the quantity of blur is equivocal. In support of this view, weak diffusers produce myopia in chicks and monkeys, the degree of which correlates with the density of the diffusers (Bartmann & Schaeffel, 1994; Smith & Hung, 2000). Furthermore, when Nevin et al. (1998) imposed a large amount of myopic defocus (−20 to −40 D) by powerful positive lenses and prevented chicks from getting close enough to objects to have sharp vision, the chicks became myopic—an anti-compensatory response. These authors concluded that some amount of sharp vision may be necessary to compensate for positive lenses, but it is equally plausible that the myopic blur experienced in this experiment was beyond the capabilities of the emmetropization mechanism and instead provoked form-deprivation myopia. In opposition to this quantity-of-blur hypothesis, there is stronger evidence that chicks can detect the sign of defocus. When chicks, wearing positive or negative lenses, were placed in circular drums for 3 h a day while under cycloplegia, and were thereby restricted to looking only at the walls of the drum 33 cm away, they compensated for positive lenses even though the viewing distance ensured 3.9 D (for +6.9 D lenses) or 12.5 D (for +15.5 D lenses) of myopic defocus (Schaeffel & Diether, 1999). Finally, if chicks are subjected to massive blur imposed by −5/+5 D cylindrical lenses (Jackson cross cylinders), they become not myopic but mildly hyperopic, implying that the total amount of blur or image degradation is not driving emmetropization (McLean & Wallman, 2003; Thibos, Cheng, Phillips, & Collins, 2001).

Our goal in this study was to further test whether the amount of defocus (without regard to sign) is sufficient to explain bi-directional lens compensation. First, we put chicks in the center of a drum, as did Schaeffel and Diether (1999), at a fixed viewing distance. When positive lenses were worn in this situation, stimuli were restricted to a plane beyond the eye's far point, which, we will argue, ensures substantial myopic blur. Our experiment differed from Schaeffel and Diether's in that we used several daily episodes of lens wear, instead of a single episode, different lens powers, more chicks and no cycloplegia. In a second experiment, we prevented sharp vision by having chicks wear weak diffusers over positive lenses. The treatments used in both experiments increased the blur experienced by the animals: chicks wearing positive lenses experienced more blur in the drum than they would in a cage because there were no nearby objects; chicks wearing diffusers suffered image degradation that could not be cleared by accommodating or looking at nearby objects. If lens compensation depends on the amount of defocus the eye experiences, then the increased defocus under both of these conditions should impair compensation for positive lenses.

2. Methods

2.1. Animals

White Leghorn chicks (*Gallus gallus domesticus*, obtained from Truslow Farms, Chestertown, MD [Hyline-W98 strain] and Cornell University, Ithaca, NY [Cornell K strain]) were reared under fluorescent lighting (14 h on, 10 h off) in heated brooders. In all experiments, chicks were initially measured at 6 or 7 days old and were measured again after 3 days of lens wear (one diffuser group in Experiment 2 was measured after 4 days, as noted in the figure).

2.2. Lenses

Lenses of +18, +10, +7, +6, −3, and −6 D made from glass or PMMA plastic, 12 mm in diameter, were glued between rigid plastic rings and Velcro support rings and then attached to mating Velcro rings glued to the feathers around the eyes (for details see Wildsoet & Wallman, 1995). Lenses were cleaned at least twice a day. If lenses or diffusers came off on more than one occasion during an experiment, those animals were removed from the experiment.

2.3. Measurements

The ultrasound biometry and measurements of refractive error were conducted while chicks were anaesthetized with 1.5% halothane (Halocarbon Laboratories) in oxygen, without cycloplegia, except when stated otherwise. Refractive error was measured using a modified Hartinger refractometer (Wallman & Adams, 1987). A-scan ultrasonography was done with a 30 MHz transducer, sampled at 100 MHz, using separate sound velocities for each axial component. We measured anterior chamber depth, lens thickness, vitreous chamber depth, and the thickness of retina, choroid and sclera (Nickla, Wildsoet, & Wallman, 1998; Wallman & Adams, 1987). Ocular length is defined here as the distance from the front of the cornea to the back of the sclera, that is the total length of the eye, instead of the more common clinical measurement of axial length from cornea to retina. Thus in our measurements, changes in choroidal thickness do not affect the ocular length, whereas they do affect conventional axial length measurements. In all experiments, the data presented are

the changes over the period of lens wear, either for each eye separately, or as interocular differences (the change in one eye minus the change in the fellow eye).

2.4. Experiments

2.4.1. Experiment 1: constant viewing distance

Each chick was restrained in a cup in the center of a drum, 60 cm in diameter, lined either with pictures taken from magazines or with an irregular geometric black and white pattern. The drums had translucent plastic lids, allowing light to enter while preventing the chicks from seeing out. The cup was positioned so that the chick was approximately equidistant from the wall, floor, and lid of the drum. To prevent chicks from falling asleep, several chicks, each in a separate drum, but in auditory contact with one another, were exposed together. In addition, the chick containers were rotated by motors at a velocity of 30 deg/s (direction switched every 30 s). Chicks were fitted with either a +6, +10, +18, −3, or −6 D lens over one eye. Because the chicks were restrained 30 cm away from the wall of the drum, the effective power of the lens was 3.3 D more negative than the values shown. Because it seemed unkind to keep the chicks restrained in the drums continuously, chicks were put in the drum for brief periods (30 min, 3 or 4 times a day), and otherwise were unrestrained in a dark, light-proof chamber. In unrestrained chicks, similar lighting regimens produce lens compensation nearly as complete as continuous lens wear (Winawer & Wallman, 2002). As there were no significant differences in the results between groups with 3 vs. 4 episodes per day in the drum, or groups with colored vs. black and white patterns, these groups are pooled throughout the paper. As controls, other animals were unrestrained in their cage, either in normal lighting or with the same light regimen and the same lenses as those in the drums.

2.4.2. Experiment 2: diffusers

To obtain different degrees in reduction of image sharpness, Bangerter occlusion foils (Ryser Optik, St. Gallen, Switzerland) of varying density were placed on top of the lenses. These lightly frosted flexible diffusers are made for use in penalizing one eye in the treatment of amblyopia. In one set of experiments, chicks were fitted with a +7 D lens plus a diffuser over one eye, and the other eye was left uncovered. In order of increasing density, the diffusers used were (as labeled by the manufacturer): "0.4" (lightest), "0.2", "0.1", "<0.1", and "≪0.1" (densest–our label). In a second set of experiments, chicks wore a +7 D lens plus a diffuser on one eye and a +7 D lens alone on the other eye. Diffusers of two different degrees ("0.2" [lighter] and "<0.1" [denser]) were used. The same type of diffusers has been used in monkeys and their effect on the human contrast sensitivity function has been described by Smith and Hung (2000). To compare the amount of image degradation produced by these diffusers and that produced by defocusing lenses, we used the contrast sensitivity data from Smith and Hung (2000), which showed that at 2 cpd the "0.4" diffuser reduced the sensitivity by 0.5 log units, and the "0.1" diffuser reduced the sensitivity by 2.3 log units. Comparable reductions would have been produced by a 3.7 D lens or a 5.2 D lens, respectively (calculations based on the modulation transfer function of an aberration-free eye, as per Bartmann & Schaeffel (1994)). Therefore, for an emmetropic chick, when both a +7 D lens and the 0.1 diffuser were worn, the image degradation attributable to the diffuser would be nearly as great as the maximum degradation by the lens (when the eye was viewing a distant object).

2.4.3. Statistics

ANOVA was used for comparisons across groups; paired two-tailed *t*-tests were used for comparisons between the experimental and fellow eyes. Because we found no significant differences between the two strains of chickens in the experiments reported here, we combined them in all data presented here. The error bars in the figures are standard errors of the mean.

3. Results

3.1. Experiment 1: chicks restrained to a constant viewing distance

3.1.1. Positive lenses

We found that eyes fitted with positive lenses grew in the compensatory direction, even when the walls were beyond their far-point. Because the wall of the drum was 30 cm away (thus presenting 3.3 D of hyperopic defocus to an unaccommodated eye), and the starting average refractive errors of the lens-wearing eyes were −1.1 D for those wearing +6 D lenses and −0.6 D for those wearing + 10 D lenses, the chicks should have initially experienced a minimum of 1.6 and 6.1 D of myopic defocus, respectively (image in front of the retina), for a chick of average refractive status, neglecting any possible accommodation. Over the 3 days of the experiment, the lens-wearing eyes shifted significantly in the hyperopic direction by 2.7 and 3.5 D, respectively, a change of 3.7 and 4.1 D with respect to the changes in the fellow eye ($p < 0.05$ and < 0.001, respectively, Fig. 1a). The change in refraction was reflected in the change in vitreous chamber depth (Fig. 1b): the normal daily increase in vitreous chamber depth was entirely inhibited in the lens-wearing eyes, resulting in a decrease of 58 μm (+6 D lenses) and 69 μm (+10 D lenses), compared to an increase of 112 or 149 μm in the untreated fellow eyes, ($p < 0.001$ for both groups, Fig. 1b).

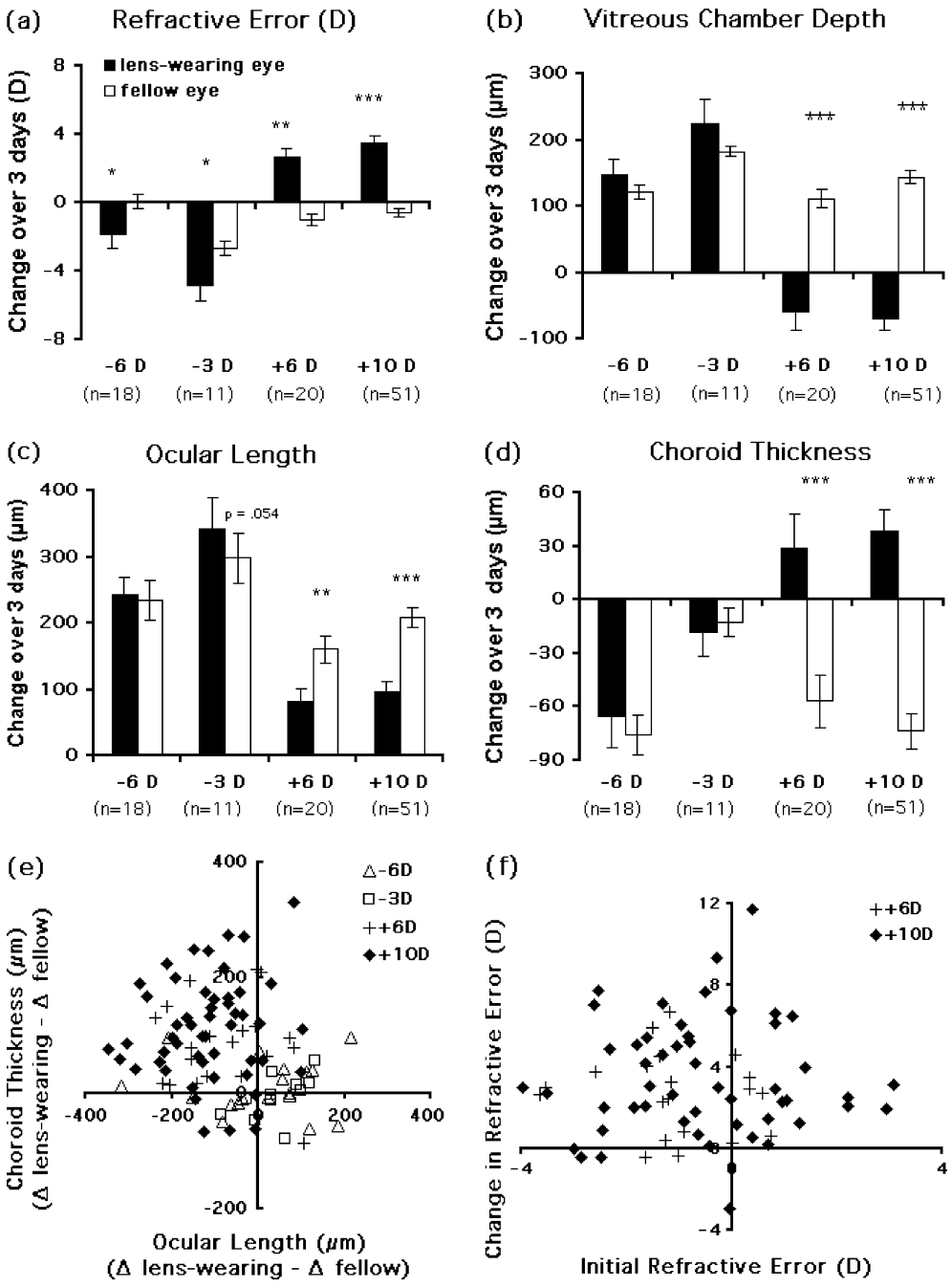

Fig. 1. Effect of wearing lenses while confined to the center of a 60 cm diameter drum: (a) for all lens powers, refractive error showed significant compensation relative to the untreated fellow eye; (b)–(d) this compensation was associated with anatomical changes in the appropriate directions in all groups, but the changes were significantly different from those in the fellow eye only in the case of eyes wearing positive lenses; (e) plot of the change in choroid thickness (change in lens-wearing eye minus that in the fellow eye) against the change in ocular length. Nearly all eyes wearing positive lenses elongated less and increased choroidal thickness more than the fellow eyes (points falling in upper left quadrant), whereas almost none of the eyes wearing negative lenses did; (f) plot of the effect of the starting refractive error on the degree of compensation for lenses worn in the drum. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

Because young chicks have a range of refractions, it is possible that even if the chicks with refractive errors near or below the mean would experience myopic defocus, those chicks with more hyperopic refractive errors might experience a focused or nearly focused view of the drum walls, and that these birds might be responsible for the overall shift towards hyperopia. Fig. 1f shows that this is not the case. There is no suggestion that the variation in amount of blur resulting from different refractive errors at the start of the experiment influenced the degree of compensation for the positive lenses (correlation coefficient = 0.00).

The shortening of the vitreous chamber in the eyes wearing positive lens was due both to a slowing of the elongation of the whole eye (a change in ocular length, as defined in Section 2.3; Fig. 1c), and to an increase in the choroidal thickness (Fig. 1d). The rate of ocular elongation was cut in half by the +6 and +10 D lenses to 81 and 97 μm, respectively, over 3 days, compared to 160 and 213 μm in the fellow eyes ($p < 0.01$ and < 0.001; Fig. 1c). The choroids thickened by 29 and 35 μm, respectively, in the +6 and +10 D lens-wearing eyes, and thinned by 57 and 76 μm, respectively, in the fellow eyes ($p < 0.001$, both groups, Fig. 1d). The thinning in the fellow eye is probably a consequence of the large amounts of darkness.

We find that the direction of compensation for positive lenses in the drum was very consistent. In 69 out of the 71 birds with positive lenses (20 with +6 D, 51 with +10 D), the refractive error shifted toward hyperopia more in the lens-wearing eye than in the fellow eye, and in 65 out of 71 birds, the vitreous chamber expanded less (or shrank more) in the lens-wearing eyes. The ocular components responsible for this vitreous chamber change were similarly consistent. In 65 out of 71 eyes the choroid thickened more in the treated eye (Fig. 1e, points above *x*-axis), and in 60 out of 71 birds the ocular length increased less (or shrank more) in the treated eyes (Fig. 1e, points to the left of the *y*-axis). Furthermore, in 55 of 71 lens-wearing eyes both the choroid became thicker and the ocular length shorter than that of the fellow eye (Fig. 1e, points in upper left quadrant). As for the fellow eyes themselves, there were no significant differences among the groups in any of the parameters measured.

3.1.2. Negative lenses

Chicks wearing negative lenses only in drums became significantly myopic in the treated eyes, although the compensation was less than with the positive lenses. Taking into consideration starting refractive errors and the distance between the chick and the walls of the drum, the chicks should have initially experienced a minimum of 6.5 and 10.5 D of hyperopic defocus for the −3 and −6 D lenses, respectively. (Because accommodation was not blocked, the amount of defocus experienced by chicks wearing negative lenses was probably less than these figures.) The change in refractive error was −2.2 and −2.0 D, respectively, relative to the fellow eye (Fig. 1a). The vitreous chamber depth and ocular length increased in the treated eyes more than the untreated eyes in both groups of negative-lens birds, though the differences were not significant (Fig. 1b).

Compensation for the negative lenses was less consistent than for the positive lenses. In contrast with the birds wearing positive lenses, most of whom both increased their choroid thickness and inhibited their axial elongation, most of the negative-lens-wearing eyes showed either increased ocular elongation or choroidal thinning, but not both (Fig. 1e). There was greater axial elongation in the treated eyes in 19 out of 29 birds with negative lenses (11 with −3 D, 18 with −6 D lenses) and thinner choroids in the treated eyes in 15 of 29 birds (Fig. 1e). Of the 29 birds wearing negative lenses seven had both greater ocular elongation and thinner choroids (Fig. 1e, points in lower right quadrant), approximately what would be expected if the two factors were independent.

Among the untreated fellow eyes, we saw no general pattern in any of the variables measured, although the −3 D group differed significantly from a few other groups (refractive error, −6 and +10 D; ocular length, +6 D; choroid thickness, +10 D), presumably because of batch-to-batch differences among the chicks used.

3.2. Comparison of lens-wearing in drums vs. cages

Lens compensation was similar whether birds were restrained in drums or free in cages (and under the same lighting regimen), implying that having the visual environment at a fixed distance did not alter the efficacy of either positive or negative lens compensation (Fig. 2): Lenses of +10 D produced a change of +4.1 D relative to the change in the fellow eye when worn in a drum and +5.1 D in a cage. The changes in vitreous chamber were also similar: 217 μm decrease in depth relative to the changes in the fellow eye in the drum vs. 213 μm in the cage. The responses to negative lenses were also not different in the drum or in the cages. The −6 D lenses produced −1.9 D of myopia when worn in the drum and −2.1 D in the cages. The vitreous chambers deepened by 24 and 31 μm, respectively, relative to the fellow eyes.

As a control for the possibility that lens compensation in the drum was driven not by the defocused images of the walls of the drum but by the sharpness of near objects (primarily, the lids of the cups that held the chicks), we put stronger positive lenses (+18 D) on chicks restrained in the drums. The stronger lenses would presumably increase the sharpness of these near objects (if indeed the chicks were looking at them) and perhaps thereby increase the magnitude of changes in the compensatory direction. Instead, we found significantly weaker compensatory changes. Wearing a +18 D lens while restrained in the drum caused only a 1.0 D hyperopic shift and a 22 μm decrease in vitreous chamber depth relative to the untreated fellow eye, whereas eyes of chicks which wore +10 D lenses in the drum became 5.1 D more hyperopic and showed a 217 μm decrease in vitreous chamber depth (Fig. 2). Because the chicks did not compensate well for the +18 D lenses in the drum, but did in the cage (a significant difference for rate of ocular elongation, $p < 0.05$), we infer that the compensation in the drum situation was not the result of the presence of near objects.

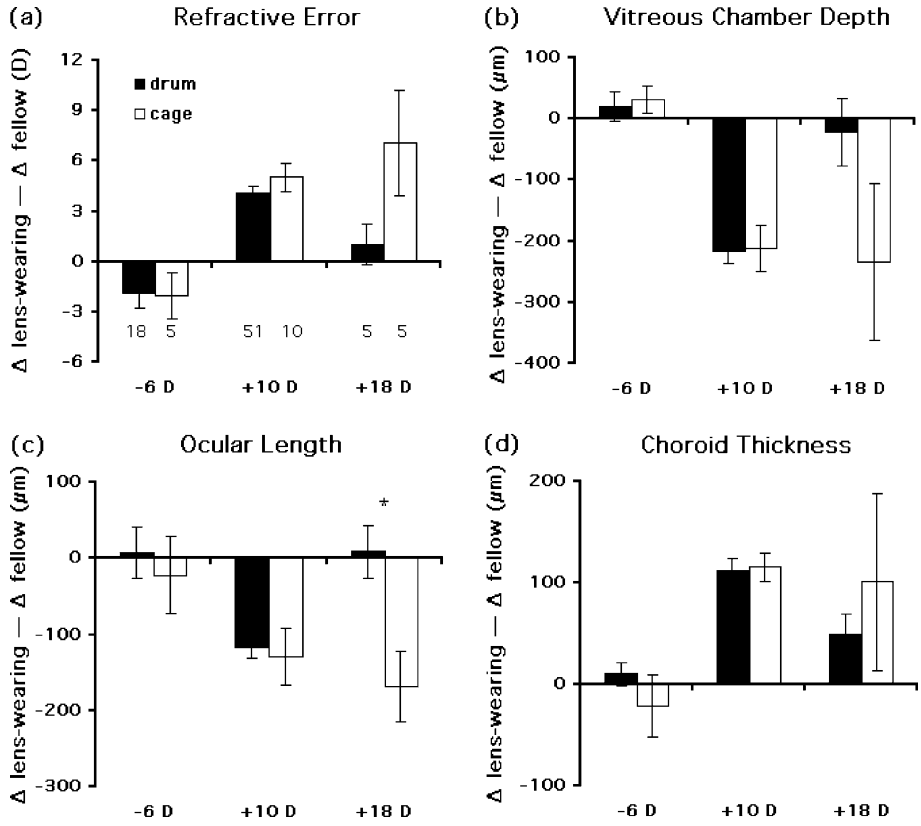

Fig. 2. Eyes showed nearly identical changes whether lenses (−6 or +10 D) were worn when birds were in the center of a 60 cm drum or unrestricted in their cages, implying that the eyes can compensate even if the images are strongly defocused. In contrast, birds wearing +18 D lenses did not compensate in the drums, but did compensate in their cages, implying that this degree of defocus of the drum walls exceeded the range of the compensatory mechanism, although the same lenses could be compensated for if close viewing was permitted. Numbers of eyes are given below bars in (a). $*p < 0.05$.

3.3. Experiment 2: lenses worn together with weak diffusers

When weak diffusers were worn on top of +7 D lenses, the refractive compensation was like that in eyes wearing lenses alone, except in the case of the densest diffusers (Fig. 3). However, diffusers of moderate densities had a surprising effect on lens compensation: they reduced the choroidal thickening normally caused by wearing positive lenses, but they enhanced the inhibition of ocular elongation. Considering that similar weak diffusers alone cause mild myopia (Bartmann & Schaeffel, 1994; McLean & Wallman, 2003), this greater inhibition of ocular elongation in the eyes wearing positive lenses together with diffusers is contrary to what would be predicted if the diffusers and the positive lenses simply had an additive effect. These conclusions are based on the results of two experiments.

First, we put diffusers of various densities over +7 D lenses. When +7 D lenses were worn with the weakest diffuser ("0.4"), the choroid thickened and the ocular elongation was inhibited to a similar degree as though the lenses had been worn alone (Fig. 3). However, with stronger diffusers ("0.1" or "0.2"), there was 74% less choroidal thickening over the 3-day experiment ($p < 0.001$, ANOVA, Fig. 3) than in eyes wearing only positive lenses (52 vs. 202 μm, respectively, both groups combined), but with a trend toward increased inhibition of the ocular elongation compared to that of eyes wearing the lens alone (−244 vs. −209 μm, respectively). An ANOVA with Bonferroni post-hoc tests showed that for the choroid response, the groups formed two distinct clusters: the groups with positive lenses and "0.2" or "0.1" diffusers had significantly less choroidal thickening than did the positive lens alone or the positive lens with the 0.4 diffuser, a phenomenon first described by McLean and Wallman (2003). In contrast, there was no significant difference among the groups with respect to ocular elongation, except that the group with the densest diffusers ("≪0.1") had more ocular elongation, as well as the other responses typical of form-deprivation: myopic refractions and thinned choroids (Fig. 3).

In contrast to the effect on compensation for positive lenses, diffusers had no significant effect on eyes wearing negative lenses (Fig. 3b). There were no differences among the groups either with respect to refractive error, ocular elongation or choroidal thickening (ANOVA, $p > 0.05$).

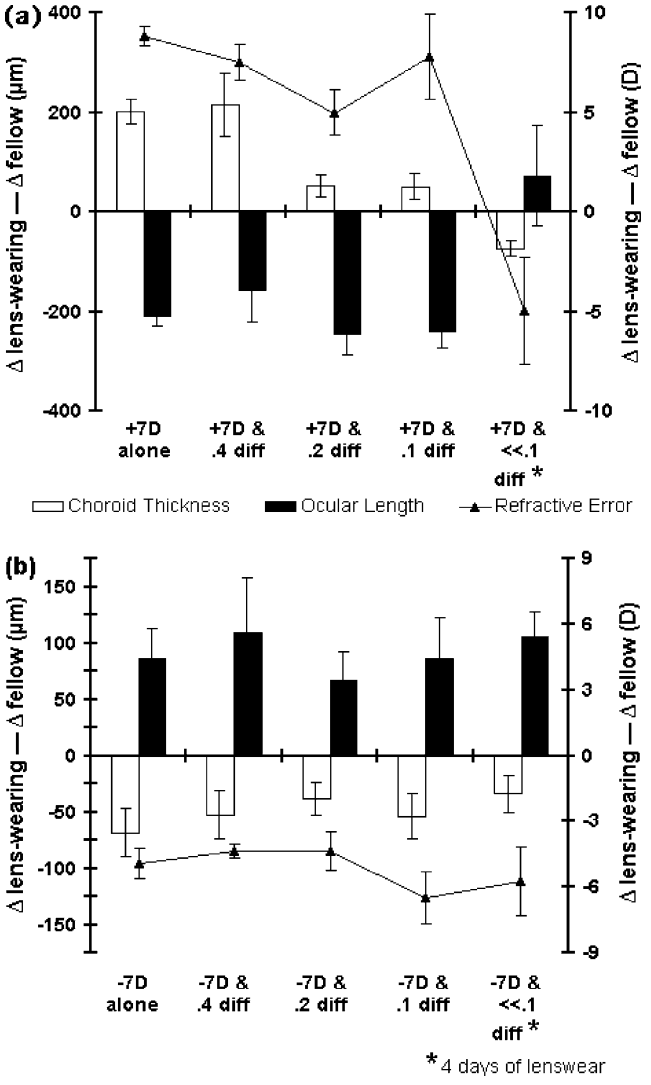

Fig. 3. Effect of combining lenses with diffusers of increasing densities. Refractive compensation (line and right-hand axis) and ocular length compensation (filled bars and left axis) are minimally affected by diffusers, except for the densest diffusers ("≪0.1") with positive lenses. However, the choroidal component (unfilled bars and left axis) of the positive-lens compensation is lost when medium-density diffusers are worn on top of positive lenses. The lower-case letters signify groups for which the changes in choroid thickness are not significantly different from those with the same letter, but are different from groups with different letters (ANOVA and Bonferroni post-hoc test). The chicks wearing the "≪0.1" diffusers were measured after 4 days, instead of 3 days.

Second, we tested more directly the suggestion from the experiment just described, that diffusers of moderate density augment the inhibitory effect of positive lenses on ocular elongation. Chicks had +7 D lenses placed over both eyes, with one eye also wearing a moderate diffuser ("<0.1" or "0.2"). There was nearly complete refractive compensation in both eyes with a small but significant difference between the two eyes (1.4 D less in eyes with diffusers, $p < 0.01$, pooled across both densities of diffusers, Fig. 4a). The compensation in the eyes wearing both positive lenses and diffusers was accomplished more by changes in ocular elongation and less by changes in choroidal thickness than is the case with eyes wearing only positive lenses. To be specific, the eyes wearing diffusers ("<0.1" or "0.2") and lenses showed about one-half as much choroidal thickening as the eyes wearing lenses alone, (84 vs. 154 μm, $p < 0.01$, Fig. 4d), but showed twice as much inhibition of ocular elongation (instead of the normal 210 μm elongation in untreated eyes, these eyes had 40 μm of elongation, a difference of 170 μm or 81% inhibition; eyes wearing positive lenses alone elongated by 102 μm, a difference of 108 μm from normal or 49% inhibition, $p < 0.001$, Fig. 4c). Because the greater ocular inhibition was mostly offset by less choroidal thickening, the differences in the vitreous chamber depth and refractive error were small.

The differential effect on choroid thickness and ocular elongation of adding a diffuser to a positive lens was very consistent across individuals. Twenty of 22 birds demonstrated a stronger inhibition of ocular elongation in the eyes with diffusers and 18 of 22 birds showed less choroidal thickening relative to the fellow eye (Fig. 4e). A total of 17 of 22 eyes wearing diffusers on top of positive lenses had both less ocular elongation and less choroidal thickening compared to their fellow eyes wearing lenses alone (Fig. 4e, lower left quadrant).

For comparison, we present data from eyes wearing diffusers alone (Fig. 4, bars on right). The eyes wearing diffusers alone had greater increases in their vitreous chambers compared to the untreated fellow eyes, but no other significant differences. From these results, it seems plausible that the lesser choroidal thickening in eyes wearing both diffusers and positive lenses might be the resultant of the separate effects of the lens and diffuser acting independently. However, the enhanced inhibition of ocular elongation cannot be explained in this way, because the diffusers alone stimulate, rather than inhibit, ocular elongation. Finally, unlike strong diffusers, which cause ever greater form-deprivation myopia as a function of time, the moderate diffusers result in little or no myopia, and in refractions which appear to quickly stabilize.

4. Discussion

Our results imply that the compensation for imposed refractive error does not depend simply on the amount of defocus. When chicks wore lenses only when restrained at a constant viewing distance beyond the far-point of the positive-lens-wearing eyes, they maintained the ability to compensate for both positive and negative lenses. Because this drum condition reverses the normal situation that we presume the chicks experience in their

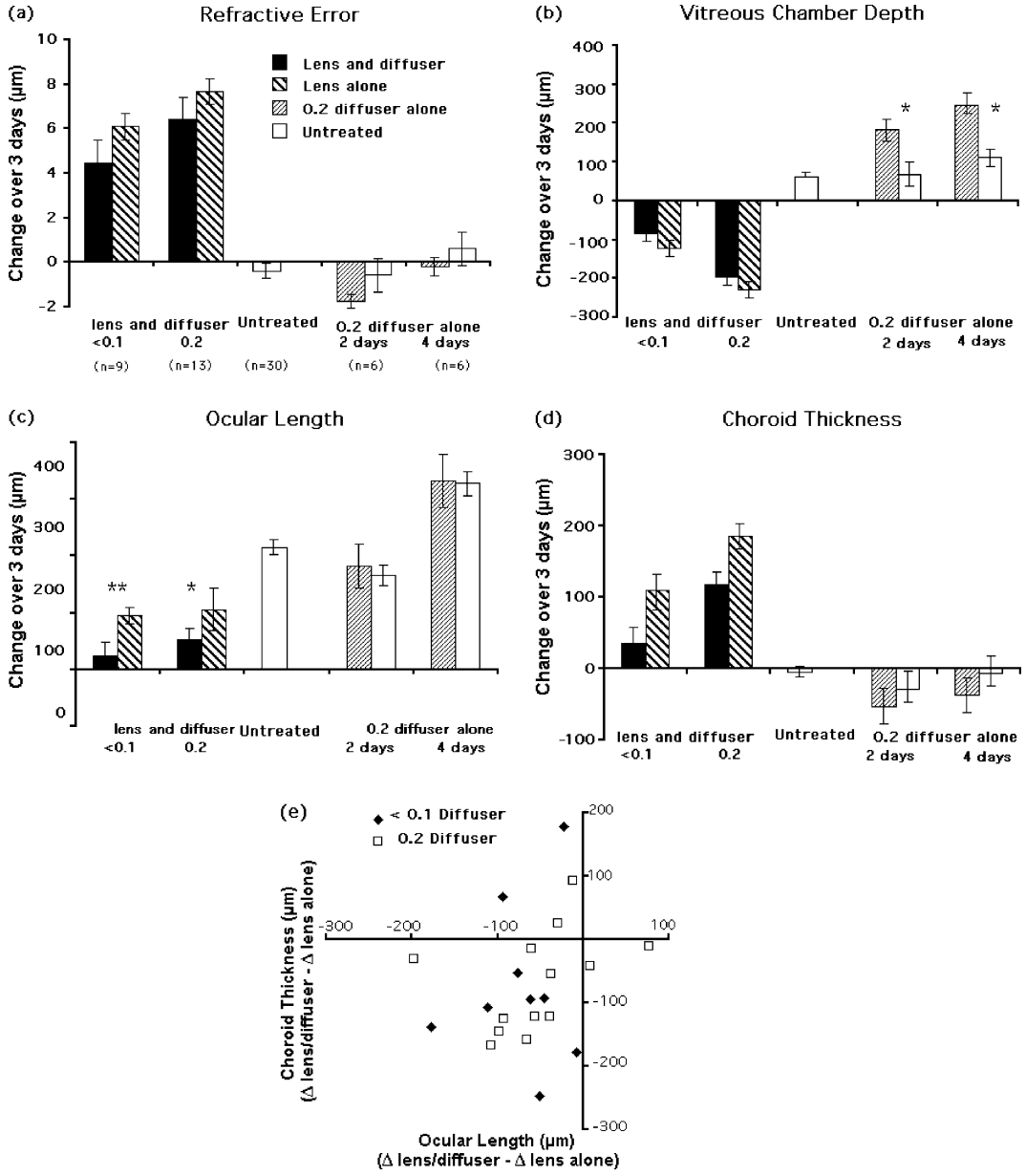

Fig. 4. Comparison of the effects of wearing a diffuser plus a +7 D lens on one eye and a +7 D lens alone on the other eye for 3 days. Refractive compensation (a) is similar in the two eyes. Ocular elongation (c), while inhibited in both eyes compared to untreated eyes, is inhibited more in the eye wearing the diffuser. Choroidal thickening (d), on the other hand, is weaker in the eyes wearing diffusers. The scatter plot in (e) shows that most eyes exhibited both less choroidal expansion and greater inhibition of ocular elongation. The bars at the right of each panel show the effects of wearing the 0.2 diffusers alone; "untreated eyes" are the untreated fellow eyes of the first three groups in Fig. 3a.

cages—of images being on average sharper if positive lenses are worn than if negative lenses are worn—we infer that the ability of chicks to respond appropriately to positive lenses does not depend on the degree of blur being reduced by the lenses. Furthermore, when the images seen through the strong positive lenses were degraded by weak diffusers, the degree of compensation did not suffer and, in fact, the ocular elongation was even more inhibited than by positive lenses alone. These results also argue that compensation for positive lenses does not require sharp images.

4.1. Lens compensation with objects beyond the far-point

The direction of compensation when positive lenses are worn in the drum situation is very consistent, implying that lens compensation (and perhaps emmetropization as well) is not simply guided by the quantity of blur. Because it is extremely difficult to measure objectively the degree of blur experienced moment-to-moment, in part because of uncertainty in how deep into the retina the measuring beam penetrates (Glickstein & Millodot, 1970; Hughes, 1979) and in part because the

direction and spatial extent of the measuring rays differ from those the eye uses in normal vision, it is therefore important to ask how confident we can be that the lens compensation in the drum situation is in fact in response to the myopically defocused image of the drum walls.

One alternative explanation would be that the lens compensation is guided, not by the image of the drum walls, but by the remaining few nearby visual features, which might be sharply focused by the strong positive lens perhaps with the aid of accommodation. Because of how the chick is restrained in the center of the drum, the only nearby visual feature available is the cover of the container that the chick is in, which is approximately 3 cm from the chick's eye. If the image of this feature were guiding lens compensation, we would expect the compensation to improve with the +18 D lens, which would enhance the sharpness of this feature. We found, to the contrary, that no significant compensation occurred for this lens in the drum, although 7 D of compensation occurred when it was worn in the cage. We interpret this finding as an indication that the near features in the drum situation are not adequate to support lens compensation and that the +18 D lens puts the walls too far out of focus to guide lens compensation.

A second alternative is that the chicks can relax accommodation to so great a degree that the walls of the drum come into focus. However, in this case, we would expect that lower-powered (+6 D) lenses would make it easier to bring the walls into focus than would higher-powered (+10 D) lenses and would therefore lead to greater compensation (hyperopia), which we do not observe. Furthermore, if sharper images led to greater hyperopia, one might expect that the untreated fellow eyes, which could easily bring the drum into sharp focus, would also grow towards hyperopia. They do not. Finally, the extent of negative accommodation documented in chicks is insufficient to clear the images in the drum situation, at least in the case of the +10 D lenses (Troilo, Lin, & Howland, 1993).

These arguments hinge on our measurement of refractive error being correct. If the eyes were much more hyperopic than our measurements indicate, our manipulations might have simply corrected a preexisting hyperopia, thereby providing sharp images rather than myopic defocus. To address this concern, we have considered four possible sources of error. First, we have confirmed that our refractometer is well-calibrated, using the two methods described in Wallman and Adams (1987). This ensures that the refractions are no more hyperopic than we report. Because of the small eye artifact (Glickstein & Millodot, 1970), which limits the accuracy of all optical refractometers, the eye could be more myopic than the refractometer measures. Errors in this direction would not mislead us into thinking we were providing myopic defocus when we were not.

Second, we considered the possibility that the more hyperopic of our chicks were able to bring the drum into focus, and that the overall changes we measured were due to these chicks pushing the average refractive change into the hyperopic direction. To test this, we correlated the refractive error at the start of the experiment with the amount of refractive change in the lens-wearing eye for birds wearing +10 D lenses. The correlation was close to zero ($r = 0.00$, Fig. 1f). Even if we compare the most myopic 20% of the birds with the most hyperopic 20%, there is no difference in the degree of compensation for the lenses (+2.7 vs. +3.2 D, respectively; $p = 0.68$). It is perhaps worth mentioning that only two of the eyes wearing +10 D lenses were more than +2.75 D, and thus could have focused the drum on their retinas, given a maximum of 4 D of negative accommodation (Troilo et al., 1993).

Third, we considered the possibility that, despite the anesthesia, the birds had a substantial accommodative tonus during the refractive measurements so that we underestimated their degree of hyperopia. To assess this we measured birds that had worn positive or negative lenses for 2 days before and after inducing cycloplegia with vecuronium bromide (Marzani & Wallman, 1997). We found that eyes that were hyperopic or emmetropic under anesthesia alone were 0.5 D more hyperopic under cycloplegia, whereas eyes that were myopic were 1.5 D more hyperopic under cycloplegia than under anesthesia alone. These results are similar to those of Schwahn and Schaeffel (1994), who found normal eyes to be 0.6 D more hyperopic under cycloplegia.

Finally, might it have been the case that the peculiar temporal pattern of lighting that we used in the drum experiments biased our results? We have four reasons for thinking that this is not a serious problem. First, the birds kept under the same lighting pattern (30 min, four times a day) in their cages showed compensation relative to the fellow, untreated eyes for both positive ($+5.1 \pm 0.8$ D, +10 D lenses) and negative lenses (-3.2 ± 0.6 D, −6 D lenses) similar to that shown by birds wearing the lenses all the time under normal lighting conditions ($+6.9 \pm 0.9$ D for +7 D lenses; -3.6 ± 0.7 D for −6 D lenses). A recent paper also found essentially normal lens compensation under intermittent illumination, with an hour or less of total daily lens wear (Winawer & Wallman, 2002). Second, the untreated eyes of these birds showed a shift (-0.7 ± 0.7 D for −6 D lenses; -1.0 ± 0.7 D for + 10 D lenses) similar to that of fellow eyes of birds wearing lenses continuously (0.3 ± 0.6 D shift for −6 D lenses; -1.3 ± 0.9 D shift for +7 D lenses), implying that the hyperopic refractions of the eyes wearing positive lenses in the drums cannot be attributed to the effect of the lighting. Third, in a small pilot experiment in which birds in the drum without defocusing lenses were compared to those with lenses, the eyes of the birds without defocusing lenses did not

differ from the fellow eyes of the birds with lenses in terms of shifts in refractive error (-2.9 ± 0.6 D, -2.5 ± 1.1 D, respectively; $p = 0.75$). Fourth, in a study conducted subsequent to this one, chicks were kept in their cages under normal lighting conditions except during their time in the drum. The lens-wearing eyes of these chicks also developed hyperopic refractions and vitreous chambers more shallow than their fellow eyes (Zhu, Winawer, & Wallman, 2003).

More generally, because in our experiments the fellow eyes unavoidably were subjected to different conditions than those experienced by the eyes of normal, untreated birds, we compared the eyes of completely normal birds to the untreated fellow eyes of birds wearing monocular positive or negative lenses, either under continuous or intermittent lighting in cages or under intermittent lighting in the drum; these comparisons showed no significant effects on either ocular length or refractive error ($p > 0.05$; ANOVA).

Although the direction of response in eyes wearing plus lenses was quite consistent, there was considerable variation in the magnitude of the effects. For birds wearing +10 D lenses in the drum, the standard deviations of the relative changes were approximately equal to the means for changes in ocular length and choroid thickness, similar to the individual variability we find in the changes in the fellow eyes alone. A substantial amount of the variability in responses may be a consequence of the very small amount of time that the birds spent in the drums, during much of which time they slept. In addition, there may be differences in the rate of lens compensation across individuals. If this were the case, extending the length of experiments might lead to more consistent responses. Finally, individual chicks, like individual monkeys, emmetropize to idiosyncratic refractions. Because we have only a single measurement before we start the lens wear, we cannot tell which eyes have reached a stable refraction and which are still moving towards their asymptote. Thus eyes at a particular refraction would show different effects of wearing lenses depending on whether they had been moving toward more myopic or more hyperopic refractions.

Our results confirm and extend the findings of Schaeffel and Diether (1999), who have also shown bidirectional lens compensation when keeping the viewing distance of chicks constant. Both sets of results show a similar degree of compensation. After their chicks wore +6.9 D lenses for 5 days, they found an interocular difference of +4.4 D; after our chicks wore +10 D lenses for 3 days, we found +4.5 D.

Our results also agree with those of Schaeffel and Diether with respect to the effect of different lens powers. They found better compensation for +6.9 D than for +15.5 D lenses, and we found no compensation for +18 D lenses, but consistent compensation for +10 and +6 D lenses. Together these results imply that lens compensation occurs over a wide range of imposed defocus, but falls off at higher degrees of defocus, reaching zero at about +15 D of imposed defocus (+18 D lens at 30 cm), although the same lens was partially compensated for when the chicks were unrestrained. These results are also consistent with those of Nevin et al. (1998), who found that +40 D lenses caused changes in the anti-compensatory direction (toward myopia) when cones around the eyes prevented the chicks from approaching objects closer than 5 cm (20–40 D of imposed defocus), but in the compensatory direction without the cones.

4.2. Effect of weak diffusers on lens compensation

We find that wearing weak or moderate diffusers over either negative or positive spectacle lenses has little effect on the degree of lens compensation. In the case of the positive lenses, essentially complete refractive compensation was attained, except in the eyes wearing the densest diffusers; in the case of the negative lenses, even these diffusers had no effect (Fig. 3). When compensation was measured by a more sensitive technique (positive lenses on both eyes, diffuser added to one eye), a small myopic shift was seen, as was the case when diffusers were worn without lenses (Fig. 4 and Bartmann & Schaeffel, 1994; McLean & Wallman, 2003; Smith & Hung, 2000). It cannot be argued that the diffusers used did not degrade the images enough to affect the emmetropization mechanism because, first, the diffusers affected the contrast sensitivity function approximately as much as a 5 D lens, second, all but the weakest diffusers had strong differential effects on the choroidal and ocular-elongation components of the compensatory response, and, third, the diffusers alone significantly increase the vitreous chamber depth (Fig. 4). Therefore, the lens-compensation mechanism appears to be able to compensate for the spherical defocus, while largely ignoring a substantial amount of image degradation caused by the diffuser.

4.3. Sign of blur versus quantity of blur

The simplest possible hypothesis of how visual input might control ocular growth would be that whenever the image is blurred or degraded, the eye is stimulated to elongate in proportion to the time that the degraded image is present. Much evidence before the present work exclude this hypothesis as feasible. Specifically, removal of lenses or diffusers for brief periods each day cancels the eye's responses in chicks (Napper et al., 1995; Schmid & Wildsoet, 1996), monkeys (Smith, Hung, Kee, & Qiao, 2002) and tree shrews (Shaikh, Siegwart, & Norton, 1999). Second, brief periods of lens wear repeated several times a day are nearly as effective as continuous lens wear (Winawer & Wallman, 2002). Third, if positive and negative lenses are worn alternately, the positive

lenses have a much stronger effect than the negative lenses (Winawer & Wallman, 2002; Winawer, Zhu, Park, & Wallman, 2000; Zhu, Winawer, Choi, & Wallman, 2002).

These findings do not, however, eliminate the possibility that emmetropization is guided by the magnitude of the blur. An anonymous reviewer of this paper hypothesized that the visual system could be guided by the duration of sharp or nearly sharp vision experienced during the day. If this period were less than a criterion amount, the eye would elongate and become myopic; if greater than this amount, it would slow its elongation and become hyperopic. The results presented here do not support this hypothesis either. First, it would seem that the birds wearing −3 D lenses over one eye and nothing over the other eye would be able to clear the images, especially given that chicks can accommodate independently in the two eyes (Schaeffel, Howland, & Farkas, 1986). These eyes would therefore be likely to have clearer vision for more time than the eyes with strong positive lenses in the drum, and yet they neither slowed their elongation, nor became hyperopic. Second, for birds wearing either +10 or −6 D lenses, the compensation in the drum was similar to that in the cage, even though birds restrained in the drum would be expected to have experienced more blur. Third, the eyes wearing +6 D lenses in the drums would have sharper images than those wearing +10 D lenses, particularly if one considers the possibility of negative accommodation bringing the eyes with +6 D into focus or nearly into focus.

Fourth, because the animals had a range of starting refractive errors, the degree of defocus they would experience in the drum would be critically dependent on these refractive errors. If the degree of blur or the duration of sharp vision were important one would expect that eyes that were more hyperopic at the start would see less blurred images for longer when wearing the positive lenses and would therefore shift more towards hyperopia compared to those that were more myopic. We did not find this association (Fig. 1f). Fifth, to see if explicitly giving the eye sharp contours would facilitate compensation, we did a pilot experiment in which birds wore lenses in the same drum, but were placed eccentrically in the drum so that they were certain to experience the walls of the drum in focus at least part of the time (distances from eye to drum walls spanned 14 to 46 cm; therefore sharply focused contours are assured for +6 D lenses; 5 min, 4 times/day). These eyes had their elongation inhibited no more than those centered in the drum (−68 μm eccentric vs. −166 μm centered), and were no more hyperopic (+1.7 D eccentric vs. +3.0 D centered). Finally, it is difficult to imagine any way in which the eyes wearing diffusers (which degrade the image by an amount comparable to 5 D of defocus) over positive lenses would not experience much more blur for longer durations than those eyes wearing lenses alone. Nonetheless, these eyes were not conspicuously less hyperopic than the eyes of the same birds that wore lenses alone, and in fact, showed significantly greater inhibition of ocular elongation (but less choroidal thickening).

As a result of these considerations, we are at a loss to explain the pattern of results presented here except by concluding that the visual system can distinguish the sign of the blur and use it to guide compensation for lenses.

4.4. Alternatives to the quantity-of-blur hypothesis for lens compensation

If the amount of blur or of sharp vision does not determine whether the eye speeds or slows its elongation, how then might lens compensation occur? Our results strengthen the case for the eye being able to detect the sign of the blur and thereby decide which way to grow. It might do this by several means. First, the eye might use the amount of accommodation as a cue to infer the sign of blur. This could be done in two ways. The eye could measure the amount of accommodation. Since hyperopes need to accommodate more than myopes, more accommodation could signal the eye to grow faster. Alternatively, the eye could correlate sharpness with the instantaneous level of accommodation. A positive correlation would signal hyperopia; a negative correlation would signal myopia. Experimental evidence shows that accommodation is not necessary for compensation: lens compensation is intact after accommodation is blocked by lesioning of the Edinger-Westphal nucleus (Schaeffel, Troilo, Wallman, & Howland, 1990) or by sectioning of the ciliary nerve (Schmid & Wildsoet, 1996) or by pharmacological blockade of accommodation (Schwahn & Schaeffel, 1994). These results imply only that accommodation does not provide the sole cue to the sign of defocus, and that the remaining cues are adequate.

Second, as mentioned in Section 1, although in a perfect optical system the direction of defocus would not be discernable in the blurred image, in biological eyes, the several aberrations combine to make the point-spread function, and hence the modulation transfer function, slightly different for defocus in the hyperopic and myopic directions, both for humans (Woods, Bradley, & Atchison, 1996) and for chickens (Coletta, Marcos, Wildsoet, & Troilo, 2003). Whether these differences can be deployed for emmetropization or accommodation is unclear, although in optimal circumstances human subjects can be trained to distinguish the sign of blurred images (Wilson, Decker, & Roorda, 2002). In addition to these so-called monochromatic aberrations, the longitudinal chromatic aberration of the eye would certainly provide a cue to sign of defocus. However, attempts to date to show less

effective lens compensation under monochromatic light have not been sucessful (Schaeffel & Howland, 1991; Wildsoet et al., 1993). Again, the negative results do not exclude the possibility that chromatic cues are used, because other cues are available as well.

Finally, the eye might grow in the correct direction by using a trial and error method, like those used by some mechanical autofocus mechanisms; that is, it might start to grow in one direction and continue if the amount of blur decreases, but reverse if the amount of blur increases (Hung & Ciuffreda, 2000). The likelihood of this being so is dim. After only 10 min of positive lens wear or 1 h of negative lens wear, one of the two compensatory mechanisms—modulation of choroid thickness—changes in the appropriate direction, when measured after an hour or two in darkness (Park, Winawer, & Wallman, 2001). It is unlikely that in 10 min the eye's refractive state would have changed enough to indicate whether the eye was growing in the wrong direction.

4.5. Why do weak diffusers have differential effects on the components of lens compensation?

Lens compensation has two components: changes in the rate of ocular elongation and changes in choroidal thickness. It is puzzling that adding a weak diffuser to a positive lens enhances the ocular elongation component (by increasing the inhibition), while decreasing the choroidal component. One can view this as evidence that there are separate visual signals guiding the two components of the response (or that there is one mechanism that controls both the choroid and the ocular length and an additional mechanism that affects only the choroid). If this were the case, in order to produce our results, these separate mechanisms would need to be sensitive to different aspects of the visual environment.

Alternatively, one can view this dissociation of the two compensatory responses as evidence that the choroidal expansion requires a stronger visual signal than does the inhibition of ocular elongation. Under normal conditions positive lenses may cause a sufficiently strong signal to stimulate maximally both the choroidal and ocular elongation responses, but when the visual signal is degraded by a diffuser, the remaining signal may be sufficient to stimulate the inhibition of ocular elongation, but not sufficient to cause choroidal expansion. A similar dissociation of the two responses occurs when brief, infrequent episodes of positive-lens wear are given, with the animal in darkness the remainder of the time (Winawer & Wallman, 2002).

Although either of these two alternatives could explain the lack of a choroid response when a diffuser is added to a positive lens, neither explains why the inhibition of elongation is enhanced. One possibility is that eyes with positive lenses alone reached full refractive compensation sooner than the eyes wearing both lenses and diffusers because of the contribution from the expanded choroid. Having re-attained functional emmetropia, the eyes with positive lenses alone would thus resume a normal rate of elongation before the end of the experiment. In contrast, the eyes wearing both lenses and diffusers might have compensated more slowly for the lens, and so the ocular elongation would have slowed over the entire 3 days of lens wear, resulting in a greater total inhibition of elongation. The plausibility of this explanation rests on the choroid responding more rapidly to imposed refractive error than does the ocular elongation (Kee, Marzani, & Wallman, 2001) and on the fact that chicks can compensate for +7 D lenses in less than 3 days.

Finally, because ocular elongation occurs by means of changes in the growth rate of the posterior sclera, we might explain the enhanced ocular inhibition by considering the physical distance between the retina and the sclera. If eyes wearing a positive lens with a diffuser have thinner choroids than eyes wearing a positive lens alone, this might mean that chemical signals traveling from the retina toward the sclera have less far to go, and therefore are more concentrated and so act more strongly.

4.6. Conclusions

The results of the two experiments presented here argue that eye growth is not directed toward myopia or hyperopia by the quantity of blur or by the duration of sharp vision. Instead, these results constitute strong evidence that the eye can discern the sign of blur and use it to guide eye growth during lens compensation and presumably during emmetropization as well. However, the definitive conclusion that the sign of defocus is used will only be widely accepted when one of the error signals employed by the emmetropization mechanism has been identified and can be manipulated to simulate the effect of myopia or hyperopia and thereby change the direction of eye growth.

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